1642

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Huylebroeck et al.

Serial No.: 10/028,396

Filed: December 21, 2001

For: NUCLEIC ACID BINDING OF MULTI-ZINC TRANSCRIPTION FACTORS

Confirmation No.: 3530

Examiner: S. Rawlings

Group Art Unit: 1642

Attorney Docket No.: 2676-5174US

CERTIFICATE OF MAILING

I hereby certify that this correspondence along with any attachments referred to or identified as being attached or enclosed is being deposited with the United States Postal Service as First Class Mail on the date of deposit shown below with sufficient postage and in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

October 6, 2004
Date

Betty Vowles
Signature

Betty Vowles
Name (Type/Print)

PETITION TO COMMISSIONER PURSUANT TO 37 CFR § 1.144

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Petitioners respectfully petition the Commissioner, pursuant to 37 CFR § 1.144, to review the requirement for restriction made final in the referenced application and direct that the requirement, with respect to the Groups identified as Groups I-IV, be withdrawn.

INTRODUCTION

37 CFR § 1.144 provides that applicants may petition the commissioner to review a requirement for restriction that has been made final. A request for reconsideration of the requirement must be presented prior to petition (see 37 CFR 1.181). Such a petition may be deferred until after the final action on or allowance of claims to the invention elected, but must

be filed not later than appeal (see 37 CFR 1.144). Petitioners requested reconsideration of the restriction requirement in the response filed November 6, 2003, which made a provisional election and traversed the restriction requirement, with respect to the Groups identified as Groups I-IV in the Communication mailed October 23, 2004, which Petitioners requested be joined and examined as a single group. The instant petition is timely filed before prosecution has closed on the elected claims.

Petitioners request the restriction requirement be withdrawn as improper with respect to the Groups identified as Groups I-IV, because the claims at issue share unity of invention and the small number of nucleotide sequences present therein is a reasonable number for inclusion in a single application.

PROCEDURAL HISTORY

A Communication was mailed October 23, 2003 by the Office containing a requirement for restriction. The Communication restricted the seventeen claims in the application into twenty-one different groups and stated that the "inventions in groups I-VIII and XIV-XXI" are "materially different methods that differ at least in objectives, method steps, reagents and/or doses and/or schedules used, response variables, assays for end products and/or results, and criteria for success, and therefore the claimed methods are distinct." (Communication mailed October 23, 2003, at page 4). The Office defined Groups I-IV as the process of providing cells with a nucleic acid sequence comprising one of the sequences selected from the group consisting of CACCTNCACCT, CACCTNAGGTG, AGGTGNCACCT, and AGGTGNAGGTG. (*Id.* at page 2). A copy of the claims at the time of the requirement for restriction is attached as Exhibit A.

Petitioners filed a response on November 6, 2003, making a provisional election and traversing the restriction requirement by requesting reconsideration thereof. By way of traversal, petitioners submitted that the Groups identified as Groups I-IV in the Communication should be joined and examined as a single group. Petitioners noted that the present invention relates to the DNA binding domain of specific zinc finger proteins, which binding domain should comprise a CACCT sequence, a spacer (N) and another CACCT sequence, or its corresponding AGGTG

sequence (*i.e.*, a downstream 5'-CACCT-3' on the complimentary DNA strand). As such, Petitioners submitted that the requirement to select a process comprising only one of the sequences (CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG) treated four configurations of the same molecule as if it were four different molecules. (Office Action response filed November 6, 2003, page 7, paragraph 4). Therefore, Petitioners asserted that Groups I-IV could not be materially different methods and restriction was improper.

In the Office Action mailed March 12, 2004, the Restriction Requirement was made final. The Office Action stated the claims were drawn to materially different methods, as the claims recite the step of providing a cell with distinct nucleic acid molecules comprising different nucleotide sequences. The Office Action asserted the different DNA sequences in the instant claims are distinct molecules and not different configurations of a single DNA sequence. Additionally, the Office Action alleged that Markush-type claims 2 and 18 encompass a plurality of distinct inventions that do not share unity of invention. (Office Action mailed March 12, 2004, page 4). Therefore, the Office Action concluded the claims were drawn on materially different methods that are distinct, lack unity of invention, and require a search that would be an undue burden. Petitioners filed an Amendment in the application on June 14, 2004 in order to timely comply with all requirements contained in the Office Action. A copy of the claims filed June 14, 2004 is attached as Exhibit B.

STATEMENT OF FACTS

The instant application discloses a method of identifying specific two-handed zinc finger transcription factors (Specification paragraph 0009). Zinc fingers are common DNA binding motifs found in eukaryotes. *Id.* at paragraph 0010. More particularly, the invention involves vertebrate transcription factors belonging to the emerging family of two-handed zinc finger transcription factors such as δEF1 and SIP1 (Smad-binding proteins). *Id.* These transcription factors contain two separated clusters of CCHH zinc fingers, which share high sequence identity (>90%). *Id.* The N-terminal and C-terminal clusters of SIP1 show high sequence homology as well, and according to the invention each binds to a CACCT sequence (SEQ ID NO: 1). *Id.* No strict requirement for the relative orientation or spacing of both sequences was observed. *Id.* For

binding to these bipartite elements, the integrity of both SIP1 zinc finger clusters is necessary, indicating that they are both involved in binding to DNA. *Id.*

This zinc finger binding strategy may be generalized to other transcription factors that contain separated clusters of zinc fingers, including other Smad-binding proteins (Specification at paragraph 0011). Moreover, the Smad-interacting protein SIP1 shows high expression in E-cadherin-negative human carcinoma cell lines, resulting in down regulation of E-cadherin transcription and possible prevention of tumor invasion and metastasis. (Specification paragraph 0011). *Id.*

The claims of the application disclose methods of identifying transcription factors such as activators and/or repressors which comprise providing cells with a nucleic acid sequence, preferably, twice the CACCT (SEQ ID NO: 1), as "bait" for the screening of a library encoding potential transcription factors and performing a specificity test to isolate the factors (Specification paragraph 0012).

ANALYSIS

Requirement for restriction is proper under 35 U.S.C. 121, if two or more independent and distinct inventions are claimed in a single application. Further, as set forth in MPEP §803, a patent application may be properly restricted to one of two or more claimed inventions only if the inventions (1) are able to support separate patents; (2) they are either independent or distinct; and (3) the examination and search of independent or distinct inventions can only be made under a serious burden.

Petitioners respectfully submit that the claims directed to the invention of the Groups identified as Groups I-IV in the Communication are not drawn to independent or distinct inventions and do not require a burdensome search. Furthermore, even if the claimed sequences were (for the sake of argument only) considered to be independent or distinct, restriction would still be improper because the claims share unity of invention and the four nucleotide sequences are a reasonable number for inclusion in a single application claim.

The Claims Directed to the Groups Identified as Groups I-IV in the Communication Are Not Independent

For purposes of a requirement for restriction, MPEP § 802.01 explains that the term "independent" means there is no disclosed relationship between the two or more subjects disclosed, *i.e.*, they are unconnected in design, operation, or effect. MPEP § 806.04(A) further explains that independent inventions are "not disclosed as capable of use together, having different modes of operation, different functions or different effects."

The instant claims disclose processes involving the use of nucleotide sequences as bait for zinc-finger transcription factors. More particularly, these claims disclose the use of nucleic acids comprising the sequences CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG as bait. These bipartite binding sites are two CACCT consensus sequences and are typical zinc finger protein binding motifs of promoter sites for genes like Brachyury, α4-integrin and E-cadherin. Furthermore, the specification, in paragraph 0070, discloses that these two CACCT consensus sequences are necessary for binding of the zinc finger transcription factors. However, the specification states that the spacing and the relative orientation of the two CACCT sequences are not critical (see Specification, paragraph 0071). As such, any of the tandem CACCT configurations bind the same specific transcription factors. Moreover, the disclosed sequences bind specific transcription factors resulting in control of genetic expression. The disclosed consensus sequences have the same bipartite protein binding design, the same operation as transcription control domains, and the same effects on expression of DNA. Consequently, the claimed process of providing a cell with these nucleic acids to identify transcription factors does not represent multiple inventions. Instead, there is a disclosed relationship between the claimed embodiments. They are dependent embodiments having the same design, operation, and effect. As such, the claimed processes using these sequences are not independent, and the restriction requirement is inappropriate.

The Claims Directed to the Groups Identified as Groups I-IV in the Communication are Not Distinct

According to the MPEP § 802.01, inventions are "distinct" if two or more subjects as

disclosed in the specification are related, but are capable of separate manufacture, use, or sale as claimed, and are patentable (novel and unobvious) over each other. If the inventions are not distinct, restriction is never proper (MPEP § 808.02).

Additionally, according to MPEP § 808.02, even if the related claims are distinct, the Examiner, in order to require restriction, has the burden of showing one or more of the following: (1) separate classification, (2) a separate status in the art when they are classified together, and (3) a different field of search. As such, if the claimed multiple inventions belong to the same classification, are in the same field of search, and there is no indication of a future change in classification and field of search, restriction is improper. The following discussion demonstrates that the claims of the Groups identified as Groups I-IV in the Communication are not separately classified, do not have a separate status in the art, are in the same field of search and, therefore, that the restriction requirement is improper.

1. The Claims of the Groups identified as Groups I-IV in the Communication are Not Separately Classified

MPEP § 808.02(A) explains that a separate classification means that each distinct invention has attained recognition in the art as a separate subject for inventive effort, and also belongs to a separate field of search. The specification of the instant application, on page 2, paragraph 0002, states that "[t]he invention relates to biotechnology generally, and more specifically to a method of identifying transcription factors." Each of the alleged multiple claimed inventions (*i.e.* processes using the sequence variously represented as CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG) are to be used as bait for potential two-handed zinc finger transcription factors. These bipartite binding sites are highly conserved zinc finger protein binding motifs found in promoter sites for genes like Brachyury, α4-integrin and E-cadherin. As such, the alleged multiple claimed inventions use sequences that belong to a specific class of transcription activating domains that bind with particular zinc finger transcription factors. Therefore, processes using these sequences are not in a separate classification, are not separate subjects for inventive efforts, and are not separate fields of search.

2. The Claims of the Groups identified as Groups I-IV in the Communication Do Not Have a Separate Status in the Art When They are Classified Together

As explained in MPEP § 808.02 (B), even though the inventions may be classified together, each subject can be shown to have formed a separate subject for inventive effort when an explanation indicates a recognition of separate inventive effort by inventors. The MPEP further explains that separate status may be shown by citing patents as evidence of such status and of a separate field of search. In the present case, no such showing is made by the Examiner. Further, the specification for the instant application gives no indication that separate inventive efforts were made by the inventors, or that separate inventive efforts were necessary for methods of each of the different sequences. Accordingly, the claims of the Groups identified as Groups I-IV do not have separate status in the art and restriction therebetween is improper.

3. The Claims of the Groups identified as Groups I-IV in the Communication Do Not Have Different Fields of Search

MPEP § 808.02(C) explains that where it is necessary to search for a distinct subject in places where no pertinent art to the other subjects exists, restriction between distinct inventions may be proper. The Office Action, on page 3, lines 21-23, asserts that a search for any one of the alleged multiple claimed inventions would not be co-extensive with the search required to examine the others. The Office Action does not indicate which different fields of search would be necessary, or if such fields of search would be pertinent to the subject matter covered by the claims.

The claims at issue in the requirement for restriction are the claims of the Groups identified as Groups I-IV in the Communication mailed October 23, 2003, set forth as claims 1-6 and 18 in the attached Exhibit B. Claim 2, as an illustrative example, includes the elements of "providing cells with a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO: 1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO: 3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO: 1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a

second SEQ ID NO: 3 separated by N) as bait wherein N is a spacer sequence."

Similarly, claim 18 includes the elements "providing cells with a nucleic acid sequence at least comprising twice a CACCT sequence (SEQ ID NO: 1) as bait for the screening of a library encoding potential transcription factors, wherein the at least twice a sequence is selected from the group consisting of CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO: 1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO: 3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO: 1 separated by N), and AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO: 3 separated by N), wherein N is a spacer sequence."

The claims are directed to a process of using a nucleic acid sequence as bait to screen for potential transcription factors. More particularly, this invention relates to the field of zinc finger transcription factors. Because the field of the invention is so specialized, it is unlikely that a search for any one of the alleged multiple inventions would "not be co-extensive with the search required to examine the others." Certainly a search required for one of the alleged multiple invention sequences (*i.e.*, CACCT-N-CACCT) that bind possible zinc finger transcription factors would be co-extensive with a search for another highly related embodiment (*i.e.*, CACCT-N-AGGTG) with the same protein binding function. Furthermore, a nucleotide database query using the CACCT consensus sequence would also query for the complimentary AGGTG sequence.

Therefore, the claims do not disclose distinct inventions. The Examiner has failed to show: (1) Separate classification, (2) A separate status in the art when they are classified together, and (3) A different field of search. As such, restriction is improper.

Even Were the Claims Directed to the Groups Identified as Groups I-IV in the Communication Considered to Be Distinct, Restriction is Improper as the Members of Markush-type claims 2 and 18 are few in number and closely related.

The Office Action mailed March 12, 2004, page 4, lines 9 and 10, alleges that claims 2 and 18 are Markush-type claims. Additionally, the Office Action, page 4, lines 11-26, alleges that it is proper to restrict Markush-type claims 2 and 18 because they encompass a "plurality of distinct inventions," requiring a "serious burden" to search, and lack unity of invention.

However, if members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, all the members of the Markush group in the claim must be examined on the merits, even where they are directed to independent and distinct inventions. (MPEP § 803.02).

Moreover, since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the office to refuse examination of Petitioners' invention, unless the subject matter in the claims lacks unity of invention. Unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility (MPEP § 803.02). This was supported by *In re Harnisch* where the CCPA suggested the concept of "unity of invention" would be "more descriptive and more intelligible internationally" than esoteric and provincial phrases such as Markush practice. *In re Harnisch,* 631 F.2d 716, 721, 206 USPQ 300 (CCPA 1980). The CCPA in *Harnisch* found that a group of "coumarin compounds," a group of dyes, shared a unity of invention because the compounds share a common utility, *i.e.*, they are all "dyestuffs," and also have a "single structural similarity" and may be grouped together in a common class which was not "repugnant to scientific classification." *In re Harnisch* 631 F.2d at 722.

Claims 2 and 18 of the instant invention (Appendix A), like the "coumarin compounds" in *Harnisch*, have unity of invention because they share a common utility and structural similarity. *Id.* In the Office Action, page 4, lines 22-26, it is asserted that claims 2 and 18 do not share a common utility because "each provides a process for identifying transcription factors, which bind to nucleic acid molecules comprising different sequences." Petitioners submit that the instant claims are directed to processes for using nucleotide sequences as bait for specific zinc-finger transcription factors. More particularly, the claims include processes using nucleic acids comprising the sequences CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG. (See *e.g.* Appendix B, claim 2). These bipartite binding sites are typical zinc finger protein binding motifs of promoter sites for genes like Brachyury, α4-integrin and E-cadherin and may be grouped in a common class that is certainly "not repugnant to scientific classification." Like the common utility shared by "dyestuffs" in *Harnisch,* these

binding sites all share a common utility of serving as transcription domains, where a class of specific zinc finger transcription factors may bind and control gene expression.

The sequences also have structural similarity. The specification discloses that these sequences are all embodiments of a particular type of bipartite CACCT binding site, comprising a pair of CACCT sequences (and/or their complimentary AGGTG sequences) separated by a spacer DNA sequence. A DNA molecule consists of two strands that wrap around each other to resemble a twisted ladder whose sides, made of sugar and phosphate molecules, are connected by rungs of chemicals called bases. Each strand is a linear arrangement of repeating similar units called nucleotides, which are each composed of one sugar, one phosphate, and a nitrogenous base. The strands run in a anti-parallel 5' to 3' orientation. Four different bases are present in DNA: adenine (A), thymine (T), cytosine (C), and guanine (G). The two DNA strands are held together by weak bonds between complimentary base pairs. Base pairs are formed according to strict pairing rules, adenine will pair only with thymine (an A- T pair) and cytosine with guanine (a C- G pair).

Applying this understanding to the 5' to 3' CACCT sequences of the instant application, there would always be a complimentary 5' to 3' AGGTG sequence. The following illustration shows the orientation of the complimentary sequence in relation to the 5' to 3' CACCT sequence:

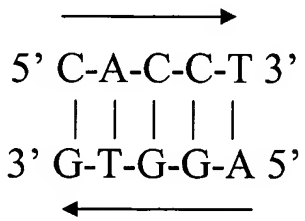

Figure 1.

Because of the anti-parallel nature of the DNA molecule and the strict base pairing rules, the above nucleic acid is identical to the following:

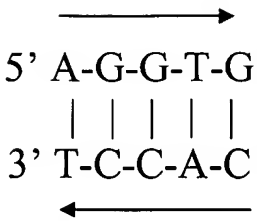

Figure 2.

Upon careful inspection it is apparent that the DNA strand in Figure 2 is actually Figure 1 flipped end-for-end.

The same phenomenon is visible in the following nucleic acids claimed in the referenced application and defined by the Office as independent and distinct Groups I-IV:

A. 5' C-A-C-C-T-N-C-A-C-C-T 3'

B. 5' C-A-C-C-T-N-A-G-G-T-G 3'

C. 5' A-G-G-T-G-N-C-A-C-C-T 3'

D. 5' A-G-G-T-G-N-A-G-G-T-G 3'

Figure 3.

Turning to sequence A, and its complimentary sequence, shown by the following representation:

A. 5' C-A-C-C-T-N-C-A-C-C-T 3'
3' G-T-G-G-A-N-G-T-G-G-A 5'

Figure 4.

and Sequence A and its complimentary sequence as it would look flipped end-for-end:

```
        5' A-G-G-T-G-N-A-G-G-T-G 3'
             | | | | | | | | | |
A.      3' T-C-C-A-C-N-T-C-C-A-C 5'
```

Figure 5.

Careful analysis of the top 5' to 3' sequence of Figure 5 reveals that this is the exact same sequence as described as sequence D in Figure 3. Therefore, because of the strict base pairing rules of DNA structure, sequences A and D are just complimentary strands of the same DNA molecule.

Structural similarities are also obvious upon close analysis of sequences B and C, from Figure 3. Sequences B and C are simple configuration changes of sequence A (effectively the same as sequence D), incorporating flipped end-for-end 5' to 3' CACCT sequences, as seen in Figures 1 and 2. As such, the nucleic acid sequences CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG are, if not the same, are very similar structurally.

Moreover, it is essential that binding sites comprise a pair of CACCT sequences to properly bind particular zinc finger transcription factors (see Specification, paragraphs 0070 and 0079). Accordingly, the sequences share substantial structural features disclosed as being essential to their common utility, *i.e.*, the common presence of paired CACCT consensus sequences and a spacer sequence, to properly bind transcription factors. Therefore, because the sequences share a common utility and have structural similarity, the sequences share unity of invention.

As such, the processes using the various sequences CACCT-N-CACCT, CACCT-N-AGGTG, AGGTG-N-CACCT and AGGTG-N-AGGTG are closely related by utility and structure, are sufficiently few in number (comprising a total of four sequences), and share unity of invention. Therefore, as stated in MPEP § 803.02, the restriction of Markush-type claims 2 and 18 is improper.

Even if the alleged multiple inventions are independent and distinct, MPEP §803.04 provides for a "reasonable number" of nucleotide sequences to be claimed in a single application.

MPEP § 803.04 sets forth:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 *et seq.* **Nevertheless, to further aid the biotechnology industry without creating an undue burden on the Office, the Commissioner has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application.** See *Examination of Patent Applications Containing Nucleotide Sequences*, 1198 O.G. 68 (November 19, 1996). (emphasis added).

MPEP § 803.04 goes on to state that "normally ten sequences constitute a reasonable number for examination purposes." Nevertheless, in the Office Action mailed March 12, 2004, on page 3, lines 23-26, the Office stated, "the Office does not presently have the resources necessary to search more than one sequence." Petitioners recognize that MPEP § 803.04 refers to sequences that encode peptides and that it may take additional resources to search for multiple nucleic acid sequences. However, only four nucleotide sequences are disclosed in the instant claims. Such a small and reasonable number of nucleic acids should not create an undue search burden. Further, searching should be coextensive as these are consensus sequences.

Petitioner respectfully requests that the Commissioner apply the reasoning of MPEP § 803.04 and allow four related sequences to be claimed in a process in a single application "to further aid the biotechnology industry." Petitioners note that requiring a restriction among these sequences, as now present in the application, will further burden the Office by requiring subsequent applications claiming the non-elected sequences.

Petitioners further note that the Office has now implemented a second pair-of-eyes review on restrictions throughout Technology Center 1600, that began with art units where either (1) the number of restrictions is particularly high, or (2) indications of poor quality restrictions were

noted in the reviews. (Announcement available through http://www.uspto.gov/web/patents/restriction1600.htm). The enhanced review procedure was effective on a limited basis as of October 2003. The instant restriction requirement issued October 23, 2003, and does not appear to have been subject to a "second pair-of-eyes" review. Petitioners respectfully submit that this petition merely requests this application receive the benefits of such enhanced review.

CONCLUSION

Because the alleged multiple inventions of Groups I-IV do not satisfy the requirements for a proper restriction, Petitioners respectfully request that the restriction requirement be removed with respect to the Groups identified as Groups I-IV, and the claims be examined on the merits.

Respectfully submitted,

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YMC/ymc

Enclosures: Petition Fee according to 37 CFR 1.17(h): $130.00
Exhibit A: clean claims submitted at the time of the November 6, 2003 response
Exhibit B: claims at the time of October 23, 2003 the restriction requirement

EXHIBIT A

(A COPY OF THE CLAIMS AT THE TIME OF THE RESTRICTION REQUIREMENT MAILED OCTOBER 23, 2003)

(Attorney Docket No.: 2676-5174US)
(Serial No.: 10/028,396)

1. A process of identifying transcription factors such as activators and/or repressors comprising:

providing cells with a nucleic acid sequence at least comprising a sequence CACCT (SEQ ID NO: 1) , preferably twice a CACCT sequence (SEQ ID NO: 1), as bait(s) for the screening of a library encoding potential transcription factors and

performing a specificity test to isolate said transcription factors.

2. A process of identifying transcription factors such as activators and/or repressors comprising:

providing cells with a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N) as bait wherein N is a spacer sequence.

3. A process according to claim 1 wherein the transcription factor comprises separated clusters of zinc fingers.

4. A process according to claim 1 wherein the sequence originates from a promoter region.

5. A process according to claim 4 wherein the promoter region is selected from the group consisting of Brachyury, a4-integrin, follistatin, and E-cadherin.

6. A transcription factor produced by the process of claim 1.

7. A process for identifying compounds with an interference capability towards transcription factors as defined in claim 6 by

adding a sample comprising a potential compound to be identified to a test system comprising: (i) a nucleotide sequence comprising one of the sequences CACCT-N-CACCT (a first_SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N) as bait wherein N is a spacer, and (ii) a protein capable to bind said nucleotide sequence,

incubating said sample in said system for a period of time sufficient to permit interaction of the compound or its derivative or counterpart thereof with said protein,

comparing the amount and/or activity of the protein bound to the nucleotide sequence before and after said adding and

identification and optionally isolation and/or purification of the compound.

8. The process according to claim 7 wherein the protein is a Smad-interacting protein.

9. The process according to claim 8, wherein said Smad-interacting protein is SIP1.

10. A compound produced by the process of claim 7.

11. The compound of claim 10, wherein said compound modifies regulation of E-cadherin expression by SIP1.

12. A pharmaceutical composition to prevent tumor invasion and/or metastasis, said pharmaceutical composition comprising:

the compound of claim 10 in an amount to prevent tumor invasion and/or metastasis in a subject, and

a pharmaceutically acceptable excipient.

13. A test kit to perform the process of claim 7, said test kit comprising:

a nucleotide sequence comprising a sequence selected from the group consisting of CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), and AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence and

(ii) a protein capable of binding said nucleotide sequence.

14. A test kit to perform the process of claim 2, said test kit comprising:

a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first_SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence.

15. A method for detecting an interaction between a first interacting protein and a second interacting protein comprising:

providing a suitable host cell with a first fusion protein comprising a first interacting protein fused to a DNA binding domain capable to bind a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first_SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence,

providing said suitable host cell with a second fusion protein comprising a second interacting protein fused to a DNA binding domain capable to bind a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first_SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N),

or AGGTG-N-AGGTG (a first_SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence,

subjecting said host cell to conditions under which the first interacting protein and the second interacting protein are brought into close proximity and determining whether a detectable gene present in the host cell and located adjacent to said nucleic acid sequence has been expressed to a greater degree than if expressed in the absence of the interaction between the first and the second interacting protein.

16. An isolated nucleic acid sequence comprising a sequence selected from the group consisting of CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), and AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer.

17. A method of identifying a new target gene, said method comprising:

identifying said new target gene using a nucleic acid sequence, said nucleic acid sequence comprising a sequence selected from the group consisting of CACCT (SEQ ID NO: 1), CACCT-N-CACCT (a first_SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer.

EXHIBIT B

(A CLEAN COPY OF THE CLAIMS SUBMITTED WITH THE AMENDMENT FILED JUNE 14, 2004)

(Attorney Docket No.: 2676-5174US)
(Serial No.: 10/028,396)

1. (Canceled)

2. (Currently Amended) A process of identifying transcription factors such as activators and/or repressors comprising:

providing cells with a nucleic acid sequence comprising a first SEQ ID NO: 1 and a second SEQ ID NO: 1 separated by N as bait, wherein N is a spacer sequence.

3. (Currently Amended) A process according to claim 2 wherein the transcription factor comprises separated clusters of zinc fingers.

4. (Currently Amended) A process according to claim 2 wherein the sequence originates from a promoter region.

5. (Original) A process according to claim 4 wherein the promoter region is selected from the group consisting of Brachyury, a4-integrin, follistatin, and E-cadherin.

6. (Canceled).

7. (Withdrawn) A process for identifying compounds with an interference capability towards transcription factors as defined in claim 6 by

adding a sample comprising a potential compound to be identified to a test system comprising: (i) a nucleotide sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N) as bait wherein N is a spacer, and (ii) a protein capable to bind said nucleotide sequence,

incubating said sample in said system for a period of time sufficient to permit interaction of the compound or its derivative or counterpart thereof with said protein,

comparing the amount and/or activity of the protein bound to the nucleotide sequence before and after said adding and

identification and optionally isolation and/or purification of the compound.

8. (Withdrawn) The process according to claim 7 wherein the protein is a Smad-interacting protein.

9. (Withdrawn) The process according to claim 8, wherein said Smad-interacting protein is SIP1.

10. (Withdrawn) A compound produced by the process of claim 7.

11. (Withdrawn) The compound of claim 10, wherein said compound modifies regulation of E-cadherin expression by SIP1.

12. (Withdrawn) A pharmaceutical composition to prevent tumor invasion and/or metastasis, said pharmaceutical composition comprising:

the compound of claim 10 in an amount to prevent tumor invasion and/or metastasis in a subject, and

a pharmaceutically acceptable excipient.

13. (Withdrawn) A test kit to perform the process of claim 7, said test kit comprising:

a nucleotide sequence comprising a sequence selected from the group consisting of CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), and AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence and

a protein capable of binding said nucleotide sequence.

14. (Withdrawn) A test kit to perform the process of claim 2, said test kit comprising:

a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence.

15. (Withdrawn) A method for detecting an interaction between a first interacting protein and a second interacting protein comprising:

providing a suitable host cell with a first fusion protein comprising a first interacting protein fused to a DNA binding domain capable to bind a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence,

providing said suitable host cell with a second fusion protein comprising a second interacting protein fused to a DNA binding domain capable to bind a nucleic acid sequence comprising one of the sequences CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer sequence,

subjecting said host cell to conditions under which the first interacting protein and the second interacting protein are brought into close proximity and determining whether a detectable gene present in the host cell and located adjacent to said nucleic acid sequence has been expressed to a greater degree than if expressed in the absence of the interaction between the first and the second interacting protein.

16. (Withdrawn) An isolated nucleic acid sequence comprising a sequence selected from the group consisting of CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), and AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer.

17. (Withdrawn) A method of identifying a new target gene, said method comprising:

identifying said new target gene using a nucleic acid sequence, said nucleic acid sequence comprising a sequence selected from the group consisting of CACCT (SEQ ID NO: 1), CACCT-N-CACCT (a first SEQ ID NO: 1 and a second SEQ ID NO:1 separated by N), CACCT-N-AGGTG (SEQ ID NO: 1 and SEQ ID NO:3 separated by N), AGGTG-N-CACCT (SEQ ID NO: 3 and SEQ ID NO:1 separated by N), or AGGTG-N-AGGTG (a first SEQ ID NO: 3 and a second SEQ ID NO:3 separated by N), wherein N is a spacer.

18. (Currently Amended) A process of identifying transcription factors such as activators and/or repressors comprising:

providing cells with a nucleic acid sequence comprising twice a CACCT sequence (SEQ ID NO: 1) as bait for the screening of a library encoding potential transcription factors, wherein the at least twice a sequence is a first SEQ ID NO: 1 and a second SEQ ID NO: 1 separated by N as bait wherein, N is a spacer sequence.

19. (New) A process of identifying transcription factors such as activators and/or repressors comprising:

providing cells with a nucleic acid sequence comprising twice a SEQ ID NO: 1, separated by a spacer sequence N, wherein each SEQ ID NO: 1 may be sense or antisense, or the complement thereof, as bait for the screening of a library encoding potential transcription factors.

20. (New) The process according to claim 19, further comprising performing a specificity test to isolate said transcription factors.